Prognostic factors in breast cancer patients evaluated by positron-emission tomography/computed tomography before neoadjuvant chemotherapy

ABSTRACT

Neoadjuvant chemotherapy (NAC) is a significant modality in breast cancer therapy. We sought to characterize prognostic factors in patients scheduled for NAC who had a pretreatment positron-emission tomography paired with diagnostic quality contrast-enhanced computed tomography (CT) (positron-emission tomography/CT [PET/CT]). A total of 118 breast cancer patients were analyzed through chart review who underwent pretreatment PET/CT imaging and received NAC from 2008 to 2014. We collected information on molecular markers, PET/CT, pathologic complete response (pCR), survival, and disease status. Pretreatment standard uptake value (SUV) max of the primary breast tumor showed no relationship to pCR; however, there was a statistically significant relationship with relapse-free survival (RFS) using univariate cox regression (P = 0.03, odds ratio (OR) = 1.06 [1.01–1.12]) with comparable findings observed with overall survival (OS). Multivariate analysis revealed SUV max to be significantly correlated with shortened OS (P = 0.022, OR = 1.08 [1.01–1.16]), with a similar trend reported for RFS. By pathological subtype, this correlation was the strongest within hormone receptor (HR+)/human epidermal growth factor receptor 2 (HER2−) tumors. In addition, Kaplan–Meier estimates demonstrated a significant difference between the RFS of triple-negative tumors and HER2 positive tumors (P = 0.001). Interestingly, within this cohort, multivariate Cox regression analysis showed HER2 positivity to be associated with favorable outcome (P = 0.04, HR = 0.22 [0.05–0.94]). These findings demonstrate a significant association between SUV max of HR+/HER2−– tumors and relapse-free and OS. Furthermore, highlighted here is the favorable survival in the once classically aggressive HER2+ breast cancer subgroup.

Keywords: Breast cancer, human epidermal growth factor receptor 2, neoadjuvant chemotherapy, positron-emission tomography, prognostic factors, standard uptake value

INTRODUCTION

Classic clinicopathologic features such as tumor stage and grade are vital in determining both treatment and prognosis of cancer patients. In addition, advances in modern imaging and disease understanding have identified other factors such as histopathological treatment response and positron-emission tomography (PET) avidity to further characterize the patient disease.[1] Unlike tumor stage and grade, these methods can provide in-treatment correlates to therapeutic efficacy; however, additional research is needed to describe the relationship between these correlates, histopathologic markers, and long-term outcome measures.

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Access this article online	
Website: www.wjnm.org	**Quick Response Code**
DOI: 10.4103/wjnm.WJNM_84_17	

How to cite this article: Farrugia MK, Wen S, Jacobson GM, Salkeni MA. Prognostic factors in breast cancer patients evaluated by positron-emission tomography/computed tomography before neoadjuvant chemotherapy. World J Nucl Med 2018;17:275-80.

PET avidity is described by the uptake of ^{18}F-fluoro-2-deoxy -D-glucose (FDG) in a target of interest normalized to the background signal within the liver or mediastinum. FDG uptake is numerically defined as the standard uptake value (SUV), with elevated SUVs generally suggestive of malignancy.[2] FDG uptake or PET avidity is used for the detection of distant metastasis in a variety of cancers, including breast, lung, colorectal, and head-and-neck.[3-6] Moreover, PET with diagnostic quality contrast-enhanced computed tomography (CT) (positron emission tomography/CT [PET/CT]) is reliable for identifying regional nodal disease involvement within breast cancer as well.[7]

In addition to staging purposes, PET avidity has been shown to have prognostic utility within a variety of malignancies, such as lymphoma, head-and-neck squamous cell carcinoma, gastric carcinoma, nonsmall cell lung cancer, and breast cancer.[8-12] Furthermore, researchers have associated the SUV of tumors with several clinicopathologic features. Previous reports demonstrated SUV max of the primary to be associated with adverse histopathologic observations in nonsmall cell lung cancer.[12] While SUV max had no prognostic utility in the head-and-neck squamous cell carcinoma, volumetric analysis of FDG uptake correlated with poor outcome.[9] Moreover, interval PET/CT scanning can be invaluable for evaluating treatment response and by extension survival-based outcome in rectal, esophageal, and head-and-neck cancers.[8,10,11,13] Similar findings were observed in breast cancer, where PET positivity following neoadjuvant chemotherapy (NAC) in preoperative breast cancer patients was inversely correlated with disease-free survival (DFS). In fact, preliminary studies demonstrated the pretreatment SUV max to be associated with shortened DFS within the molecular and pathological subtypes of breast cancer.[14-17] Nevertheless, further work is needed on the association of pretreatment FDG uptake and therapeutic response, as well as other clinically relevant endpoints.

One histopathological method to assess therapeutic efficacy is pathologic complete response (pCR). Esserman *et al*., described pCR in breast cancer as the absence of pathologically-detected malignant cells from the surgically resected primary site and relevant lymph nodes following NAC.[1] Patients that achieve pCR have significantly improved survival-based outcomes compared to patients with a residual tumor on resection. A similar relationship between pCR and prognosis has been observed in multiple cancers, including rectal and esophageal cancers.[13,18,19] Moreover, pCR is currently being used as a surrogate endpoint for evaluating potential new therapies within breast cancer.[1] Paradoxically, it is typical to observe higher pCR rates within intrinsically aggressive cancer subtypes, including high-grade tumors, triple-negative breast cancer (TNBC), and human epidermal growth factor receptor 2 (HER2) positive breast cancer.[20] By comparison, patients with hormone-receptor-positive (i.e., estrogen receptor and/or progesterone receptor positive) (hormone receptor [HR]) and HER2 negative breast cancer are less likely to achieve pCR despite classically being more indolent. As FDG uptake reflects tumor characteristics such as metabolic activity, it is possible PET avidity informs the pCR rate of breast cancer. Several studies have examined the relationship between FDG uptake and treatment response in a variety of malignancies, most commonly by comparing pretreatment PET/CT imaging to interval scans during cycles of chemotherapy, then ultimately to tissue pathology at resection.[21-23] In this setting, reductions in PET avidity during treatment were correlated with lower burdens of residual disease, or in some cases pCR. In the current study, we investigated the prognostic utility of pretreatment SUV max in breast cancer and how it correlates with the pCR rates. In addition, we also evaluated survival-based outcome measures within the pathological subtypes of breast cancer.

METHODS

Positron-emission tomography/computed tomography
Patients were fasting for at least 4 h before the procedure. Between 370 MBq and 425 MBq intravenous FDG was given and imaging was performed 1 h later. Images were obtained from the base of skull to thigh. SUV max was calculated using Syngo.via (Siemens)

Pathological examination
Following NAC, patients underwent either a modified radical mastectomy or lumpectomy, followed by an axillary lymph node dissection or sentinel node biopsy when appropriate. Nottingham criterion determined the overall histologic grade. Patients were clinically staged according to the American Joint Committee on Cancer 8th edition (AJCC). Pathologic complete response was defined as the absence of microscopically detected malignant cells in the resection bed of the primary lesion as well as the resected lymph nodes, ypT0/ypN0. Estrogen receptor or progesterone receptor positivity was defined as $\geq 1\%$ of positive cells by immunohistochemistry. HER2 positivity was defined as $3+$ by immunohistochemistry or fluorescence *in situ* hybridization ratio >2.2. Relapse was defined as pathologically confirmed recurrent disease or findings on advanced imaging within reasonable clinical suspicion if biopsy could not be performed.

Statistical analysis
Data analyses were performed using IBM SPSS Statistics version 21 IBM Analytics (Armonk, New York, USA) along

with Graphpad Prism 5.0 for figure construction. For survival analysis, univariate Cox regression and multivariate Cox regression were performed. Associations between SUV max and pCR was determined using Spearman's correlation. Log-rank test with *post hoc* pairwise comparisons was performed to evaluate outcome measures between the pathological subtypes. Significance was determined using the value of $P < 0.05$.

RESULTS

We retrospectively evaluated 927 female breast cancer patients, ultimately analyzing 118 who had pretreatment PET/CT imaging and received NAC from 2008 to 2014 [Figure 1 and Table 1]. Within this cohort, the mean and median age was 51 years (range 23–82) and mean follow-up was 50.25 months, median was 44 months (range 7.3–101.5); nearly 47% were AJCC Stage II, 53% Stage III; 6% were Grade 1, 42% Grade 2, and 49% Grade 3. Tumor grade was not reported in three patients. The pathological subtypes of these breast cancers were 52% HR+/HER2−, 31% HER2 positive, and 17% TNBC. About 92.5% with HER2 positive tumors received NAC containing at least one HER2 targeted agent, with a full description of NAC regimens in Supplemental Table 1. Of these patients, 18% relapsed and 11% died over this period.

The SUV max of 109 primary breast tumors was analyzed with a mean of 8.9 ± 6.8. The SUV max from nine primary tumors could not be obtained. SUV max of the primary breast tumor was significantly associated with relapse-free survival (RFS) by univariate cox regression ($P = 0.03$, odds ratio (OR) = 1.06 (1.01–1.12)) with similar findings observed with overall survival (OS) ($P = 0.009$, OR = 1.07 [1.02–1.13]) [Figure 2]. Moreover, multivariate analysis, including grade and stage of disease found SUV max to be significantly correlated with shortened OS ($P = 0.022$, OR = 1.08 [1.01–1.16]), with a similar trend reported for RFS ($P = 0.057$, OR = 1.06 [0.99–1.1]) [Figure 2]. In patients with HR+/HER2− tumors, SUV max demonstrated a significant relationship with both RFS ($P = 0.019$, OR = 1.10 [1.02–1.19]) and OS ($P = 0.003$, OR = 1.14 [1.04–1.24]) through univariate regression [Figure 2]. Multivariate cox regression, which included SUV max, tumor stage, and grade, found significant associations between SUV max of HR+/HER2− tumors and both outcome measures (RFS: $P = 0.046$, OR = 1.00–1.19); OS: ($P = 0.02$ OR = 1.12 [1.02–1.23]) [Figure 2]. No significant associations between SUV max and outcome were observed for TNBC or HER2+ disease.

Overall pCR rate, defined as ypT0/ypN0, was 19.5%, with rates of 15%, 8.2%, and 40.5% observed in the TNBC, HR+/HER2−, and HER2+ groups, respectively [Table 2]. Consistent with

Table 1: Description of patient cohort

		Mean	N
Age (years)		50.86	
Follow up (months)		50.25	
Stage	Stage II		55
	Stage III		63
Grade	Grade 1		7
	Grade 2		50
	Grade 3		58
Subtype	TNBC		20
	HR+/HER2-		61
	HER2+		37
Relapse	No relapse		97
	Relapse		21
Vital status	Alive		105
	Dead		13

Table 2: Standard uptake value and pathologic complete response

	Overall	TNBC	HR+/HER2-	HER2+
SUV max				
Mean±std	8.9 ±6.8	12.1 ±9.1	8.3 ±6.7	8.4 ±4.6
pCR				
% of total	19.5	15	8.2	40.5

prior studies, pCR was associated with the favorable outcome overall and all three subtypes [Supplemental Figure 1]. FDG uptake had no significant association with pathologic complete response by Spearman's correlation ($R = 0.128$, $P = 0.186$).

Log-rank analysis with *post hoc* pairwise comparisons showed a significant difference between the RFS of triple-negative tumors and HER2 positive tumors ($P = 0.001$), while the comparison between HR-positive/HER2 negative and HER2 positive was not statistically significant ($P = 0.12$) [Figure 3]. Similar findings were observed with OS [Figure 3]. Multivariate cox regression analysis including grade and stage of tumors showed HER2 positivity to be significantly associated with a lengthened RFS ($P = 0.04$, HR = 0.22 [0.05–0.94]); however, no statistically significant association with OS was observed ($P = 0.182$, OR = 0.42 [0.03–1.94]). Of note, tumor grade was significantly related to RFS ($P = 0.039$, OR = 2.60 [1.05–6.46]) and OS ($P = 0.028$, OR = 5.28 [1.19–23.2]), whereas clinical stage was not predictive in this context.

DISCUSSION

Advancing technology and understanding of cancer have ushered in new ways to complement traditional
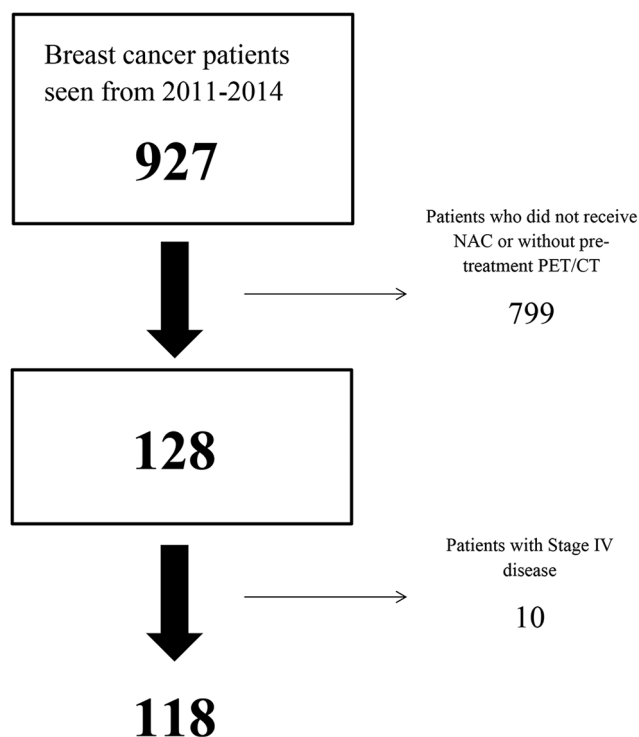
Figure 1: Flow diagram for patient selection. Charts of 927 patients were reviewed. 128 were scheduled for neoadjuvant chemotherapy and had pretreatment positron emission tomography/computed tomography imaging. Of these patients, 10 with Stage IV disease were excluded

	RFS	p	OR	95% CI	OS	p	OR	95% CI
Univariate Analysis								
SUV-All tumors		0.03	1.06	1.01-1.12		0.008	1.07	1.02-1.13
HR+/HER2-		0.019	1.1	1.02-1.19		0.02	1.12	1.02-1.23
HER2+		0.841	1.04	0.72-1.49		0.75	0.99	0.90-1.08
TNBC		0.824	0.99	0.91-1.08		0.75	0.99	0.90-1.08
Multivariate Analysis								
Stage		0.167	1.99	0.75-5.28		0.382	1.67	0.53-5.3
Grade		0.041	2.67	1.04-6.81		0.031	4.5	1.14-17.7
SUV-All tumors		0.057	1.06	0.99-1.13		0.008	1.07	1.02-1.13
HR+/HER2-		0.046	1.09	1.00-1.19		0.02	1.12	1.02-1.23
HER2+		0.63	1.8	0.17-18.9		0.98	0.95	0.28-31.89
TNBC		0.667	1.02	0.92-1.15		0.64	1.03	0.90-1.19

Figure 2: Association between pretreatment standard uptake value max and outcome. Univariate cox regression was performed comparing standard uptake value as continuous data with relapse-free survival or overall survival. Multivariate cox regression was performed similarly, including tumor stage and grade within the analysis. Significance was determined by $P < 0.05$

clinicopathologic classifications, thus aiding in the characterization of human disease. Previous reports have found numerous approaches in which FDG avidity can be incorporated into the prognostic portrait of a patient.[8-13] Indeed, in this cohort primary SUV, max was significantly associated with poor outcome [Figure 2]. However, given the weak OR of this finding, it is unlikely to be of any real prognostic utility. Therefore, in the setting of all breast cancers, it is unlikely that primary SUV max could substantially contribute to the prognostic portrait of the patient. Previous studies have reported the prognostic value of SUV max within the molecular and pathological subtypes of breast cancer, particularly HR+/HER2− and TNBC.[14,17] In the agreement, in our data, the association between primary SUV max and survival was differentially strongest within the HR+/HER2− subtype [Figure 1], with no statistically significant relationships, observed within the HER2+ or TNBC groups for either endpoint.[24] Patients with HR+/HER2− generally do very well within the short-term. However the propensity of these tumors to reoccur distally, often many years past diagnosis and treatment, can make providing long-term prognostic outlooks challenging.[25] Therefore, incorporating SUV max of the primary into the clinical picture is most attractive for patients with HR+/HER2− disease and may further enhance outcome predictions within this subset of patients.

The relationship between FDG uptake and pCR has primarily been studied in the context of comparing pre- and post-treatment avidity. Researchers have used the change in SUV-based metrics to determine the future efficacy of a chemotherapeutic regimen as well as predicting the presence (or absence) of residual disease on surgical resection.[26-29] In the current study, pretreatment SUV max alone had no predictive value for pCR, suggesting that baseline metabolic characteristics are not closely associated with chemosensitivity in this population.

Prior reports observed that pCR can achieved within the HER2+ positive tumors treated with trastuzumab in 30%–50% of patients, whereas generally HR+/HER2− and TNBC tumors respond completely in up to 8%–16% and 33% of patients, respectively.[20] Consistent with prior findings, pCR rates in our study within the HER2+ and HR+/HER2− tumors was 40.5% and 8.2%, respectively. However, only 15% of patients with TNBC tumors achieved pCR in this report. The reason for this discrepancy is unclear, likely in part impacted by the relatively low number of TNBC patients in the cohort.

By comparison, the long-term outcomes of patients within this cohort were better than expected. A majority of patients studied presented with Stage III disease (53%), yet there were only 21 (18%) relapses and 13 (11%) deaths. In particular, patients with HER2+ disease fared, especially well with only two observed relapses and one death during the follow-up period, with an estimated RFS of 96% at 3 years, 91% at 5 years. Other studies which compared regimens with or without trastuzumab for patients with HER2 positive disease demonstrated a 3-year event-free survival (EFS) of 88% within the trastuzumab-containing arm.[30] In addition, the NeoALTTO trial which examined
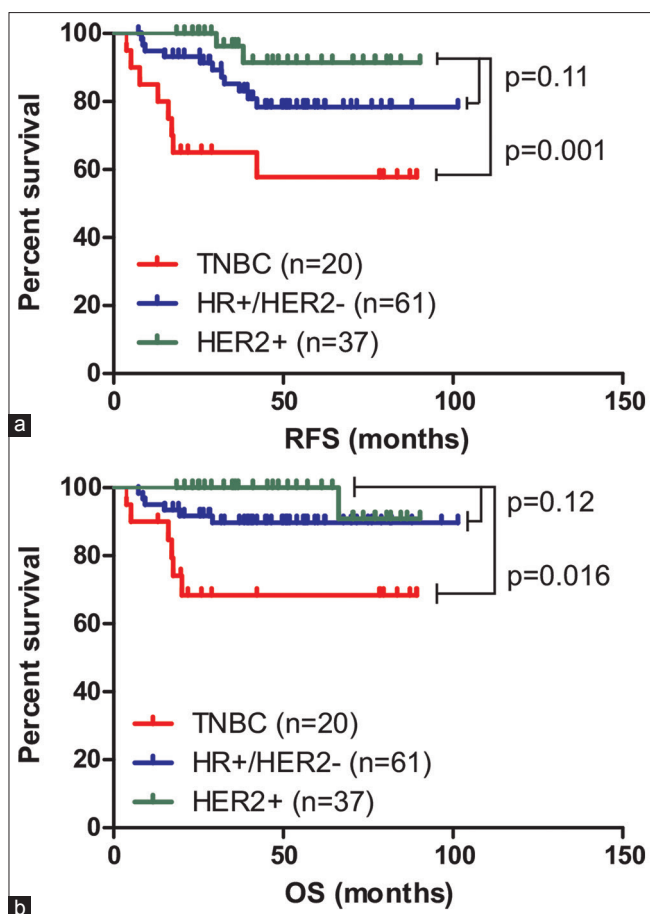
Figure 3: A comparative analysis between survival and pathologic subtype of patients. (a) Log-rank test with *post hoc* pairwise comparisons between the pathologic subtypes for relapse-free survival. (b) Log-rank test with *post hoc* pairwise comparisons between the pathologic subtypes for overall survival. Significance was determined by *P* < 0.05

three different anti-HER2 regimens reported EFS at 3 years to be 76%–84%.[31]

CONCLUSION

Limitations of this study include biases inherent to all retrospective studies, and the fact data were collected from a single institution, subsequently restricting a broader application for these findings. Nevertheless, this report has documented several interesting conclusions. We have examined the prognostic utility of pretreatment SUVs, revealing a potential role in patients with HR+/HER2− tumors. Furthermore, there was no apparent connection between pretreatment FDG uptake and pCR following NAC. Finally, the survival measures for patients with HER2+ breast cancer were markedly improved as compared to previous data, exemplifying the efficacy of targeted therapy.

Conflicts of interest
There are no conflicts of interest.

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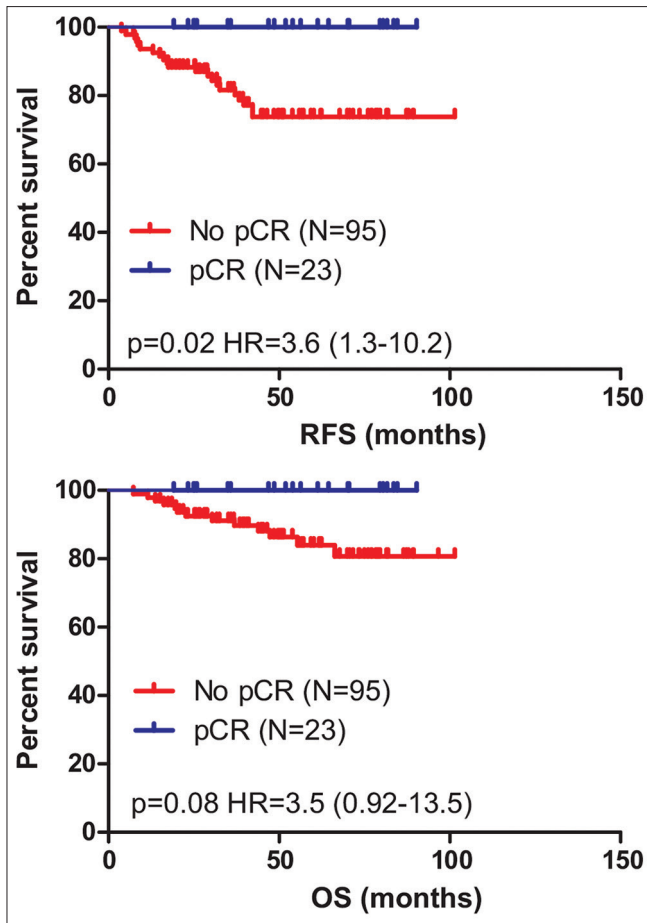
Supplemental Figure 1: Association between pCR and survival

Supplemental Table 1: Neoadjuvant chemotherapy regimens

					NAC						Total
	Not reported	TC	AC + T	AC + T + other	AC	TCH	TCHP	AC + TH (or other anti-HER2)	AC + TH + another anti-HER2	Other regimen	
Subtype analysis											
TNBC	1	0	11	4	3	0	0	0	0	1	20
HR+/HER2−	2	9	39	3	4	1	1	0	1	1	61
HER2+	0	1	2	0	0	4	8	18	3	1	37
Total	3	10	52	7	7	5	9	18	4	3	118

TNBC: Triple-negative breast cancer; HER2: Human epidermal growth factor receptor-2; HR: Hormone receptor; NAC: Neoadjuvant chemotherapy; TC: Paclitaxel carboplatin; AC: Adriamycin carboplatin; T: Paclitaxel; TCH: Paclitaxel carboplatin trastuzumab; TCHP: Paclitaxel carboplatin trastuzumab pertruzumab; TH: Paclitaxel trastuzumab